Remarks

Introduction

Claims 5-6, 8-10, 12-13, and 18-25 are under examination. Only one rejection remains. The Office alleges the claims are obvious over the combination of Houben et al., Trading et al., and Unger et al.

The present invention arises in part from the counterintuitive realization that administration of a basal replacement dose of glucagon to a patient taking insulin achieves the beneficial effect of preventing hypoglycemia by virtue of the buffering or blunting effects of glucagon without diminishing the beneficial effects of glucose regulation provided by insulin (see the specification at paragraph [0018] et seq.). The basal replacement dose is administered when the patient in a euglycemic state rather than to a patient in or entering a hypoglycemic state. The basal replacement dose of glucagon administered is significantly lower than conventional doses administered for treatment of insulin-induced hypoglycemia.

Rejections Under 35 USC 102(e)

Applicants acknowledge with gratitude the withdrawal of the rejection under 35 USC 102(e) in view of U.S. Pat. No. 6,572,542 to Houben *et al.* (hereinafter "Houben").

Rejections Under 35 USC 103(a)

All of the claims were rejected as obvious in view of Houben in combination with Trading et al. and Unger et al. Applicants respectfully traverse the rejections.

A. Houben did not describe the claimed invention, as evidenced by the Office's acknowledgement that Houben is not anticipatory, and the Trading and Unger references do not suggest any modification of Houben relevant to the claimed invention.

As set forth at length in Applicants' prior response, Houben describes a system for using an ECG/EEG sensor to determine that a patient "has entered" or is "about to enter" a hypoglycemic state. According to the teachings of Houben, ECG/EEG signals are analyzed by a microprocessor and, based on the analysis, an agent such as insulin or glucagon may be

administered to modify the patient's blood glucose level. Houben differs from the present invention in many respects. For example, Houben does not suggest administration of a basal replacement dose of glucagon and does not suggest administration of glucagon to patients when they are euglycemic, as part of an ongoing treatment regimen to prevent (or reduce the incidence of) hypoglycemia. Houben relates instead to the rescue of a patient for whom a hypoglycemic event has occurred or is imminent.

The Office has correctly acknowledged that the Houben reference does not anticipate the claimed invention. Therefore, to establish *prima facie* obviousness the Office must explain why one of ordinary skill in the art would have modified the teachings of Houben to arrive at Applicants' invention.[1] The Office has not done this. Clearly neither of the secondary references cited by the Office suggests anything that would have motivated one of ordinary skill in the art at the time the present invention was made to modify Houben so as to arrive at the invention. Trading et al. ("Trading") describes a long acting glucagon. Unger et al. ("Unger") describes a general method for formulation encapsulation of therapeutic agents, such as glucagon. The Office has pointed to no basis in any of the cited references as to why one might be motivated to use a long-acting or encapsulated glucagon in the Houben system or vice versa (to use the Houben system in combination with a long-acting or encapsulated glucagon). The Applicants also respectfully submit that the Office has cited no evidence that suggests those of ordinary skill in the art would be motivated to use the Houben device in the first instance; indeed, the record is silent as to whether the device has ever been recognized outside of the patent itself as useful or practical for monitoring diabetic patients.

Nonetheless, assuming, *arguendo*, that one of skill would have combined the teachings of Houben, Trading and Unger the result would not be Applicants' invention, but merely a system for using an ECG/EEG sensor and microprocessor to determine that a patient "has entered" or is

[1] "To establish a *prima facie* case for obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." See MPEP 706.02

"about to enter" a hypoglycemic state and, based on the analysis, administer glucagon, optionally a long-acting glucagon or glucagon formulated in microspheres, liposomes or liposomal microspheres, to modify the patient's blood glucose level. Nothing in this combination of references would lead one of skill to practice the instant invention. Nothing in this combination of references would lead one of skill to administer a basal replacement dose to a patient who is not manifesting symptoms of hypoglycemia.

B. Houben did not describe the claimed invention, as evidenced by the Office's acknowledgement that Houben is not anticipatory, and nothing in the Trading and Unger references remedy this deficiency, as shown above. The Office Action provides no evidence or scientific reasoning in support of the obviousness rejection.

Insofar as the Office has acknowledged that Houben did not anticipate any claim, and insofar as it is clear that the Trading and Unger references relate to long-acting and encapsulated forms of drugs such as glucagon, and that only claims 10, 12 and 13 even mention such forms of glucagon, the basis for the Office's allegation of obviousness appears to arise from hindsight reconstruction of the invention.

The Office Action appears to suggest that one of skill reading Houben would be motivated to use a "combination approach" because Houben "advantageously teach[es] use of an insulin/glucagon infusion pump for *treating* hypoglycemia . . . " (page 4; emphasis added). The Office Action further appears to suggest that, given the motivation to use the "combination approach," it would have been trivial for one of skill to arrive at Applicants' invention.

First, it is unclear what "combination approach" the Office believes is taught by Houben. It has long been known to administer insulin to diabetic patients to avoid hyperglycemia, and it has long been known to administer glucagon to treat insulin-induced hypoglycemia. Houben does not teach a new use of either of these agents, but instead teaches a method for detecting actual or impending hyper- or hypo-glycemia:

> In the system of the present invention, it is specifically contemplated that the system have the capability to deliver more than one type of beneficial agent to a patient. For example, if the patient is diabetic and prone to

> episodes of hypoglycemia and hyperglycemia, then the system of the present invention may be configured to deliver, for example, glucagon, diazoxide or glucose during or just prior to a hypoglycemic event, as well as to deliver insulin or a sulfonylurea-based drug during a hyperglycemic event. Additionally, the system of the present invention is not limited to systems having the capability of detecting or sensing hypoglycemia, but includes within its scope systems having the capability of detecting or sensing hyperglycemia.

Houben at col. 14, lines 10-22. Nothing in Houben suggests any of the instant claims, which include, for example, administration of a basal replacement dose to a patient with a euglycemic blood glucose level of 70-110 mg/dL (see, e.g., claim 9) or administration of glucagon to a patient with a euglycemic blood glucose level of 70-110 mg/dL as part of a regular (e.g., daily at bedtime) diabetes treatment regimen to prevent or reduce the risk of insulin-induced hypoglycemia (see, e.g., claims 21 -22).

The Office Action appears to suggest that, because diabetes is an "age old disease," well studied and widely treated, the Office believes that *any* method of therapy or prophylaxis using insulin or glucagon is presumptively only routine optimization of known therapies. See Office Action, at bottom of page 4. The Office Action states that one of skill would have been motivated to use a "combination approach to balance this well-known disease of diabetes, wherein both insulin and glucagons levels must be maintained in balance; including any patient specific amounts . . . which doctors or pharmacists are charged with routinely optimizing . . . ." *Ibid.* In response, Applicants respectfully submit that:

- the Office Action seems to based on the mistaken impression that the present invention is based on administration of "patient specific amounts"; and

- even assuming one of skill would have been motivated to maintain "insulin and glucagon levels . . . in balance,"[2] this assumption would not relieve the Office of the obligation to explain *why* the prior art or common knowledge would result in Applicants'

[2] Applicants do not know what specifically is meant by the Office by the phrase "in balance." Should any rejection be maintained, clarification is respectfully requested.

claimed invention. Assuming a well known *need* to find ways to maintain "insulin and glucagon levels . . . in balance" does not mean that new and innovative methods for accomplishing this would have been obvious. Indeed, the pressing need for new approaches for an "age old disease" is evidence that current therapies are inadequate and new approaches are not obvious.

The Office Action states one of ordinary skill would be motivated to use insulin or glucagon in "patient specific amounts" and that that "doctors or pharmacists are charged with routinely optimizing for the patient in question." The Office appears to have misunderstood the invention. A basal replacement dose of glucagon is not a "patient specific" dose but rather describes a type of administration of glucagon at doses not previously used to treat hypoglycemic events. Normal basal glucagon levels in adult humans are about 50 to 150 picograms/ml plasma. The present specification teaches that when glucagon is administered by intravenous infusion, basal glucagon levels are achieved in an adult patient by infusion of glucagon at a rate in the range 0.10 ng/kg/min to 5.00 ng/kg/min (see the instant specification at, e.g., paragraph [0027] and current claims 18, 24 and 25). As explained in Applicants' prior submission:

> Claim 5, as amended, is directed to a method of reducing the risk of insulin-induced hypoglycemia by administering a *basal replacement dose* of glucagon to a patient. The goal is to provide a level of plasma glucagon approximating the normal basal level (about 50 to 150 picograms/ml plasma) and prevent an unopposed action of insulin (see, e.g., paragraph [0066]). As taught in the specification, a basal replacement dose can be delivered by intravenous infusion of glucagon at 0.10 to 5.00 ng glucagon/kg patient weight/min (see paragraphs [0027] and [0028]). Alternatively, a basal replacement dose of glucagon can be given by other routes (e.g., subcutaneously or intramuscularly).
>
> The basal replacement dose is quite low (e.g., 0.4 - 21 micrograms per hour for a 70 kg patient receiving an infusion) and not taught or suggested by the '442 patent. The '442 patent does not specify *any* particular dose of glucagon, and, accordingly, would be understand by one of skill in the art to refer to administration of the *conventional* (e.g., 1 mg) dose of glucagon normally administered to patients to treat hypoglycemia. Administration of a conventional dose results in plasma glucagon that peaks at about 8

> nanograms/ml (see, paragraph [0053]) while glucagon administration according to the present invention results in plasma glucagon concentrations in the picogram range. The '442 patent did not describe and would not have led one of ordinary skill to the claimed method. Accordingly this rejection should be withdrawn.

The Office has not, and cannot, provide any evidence or sound reasoning that administration of a basal replacement dose (claim 5) is mere optimization.

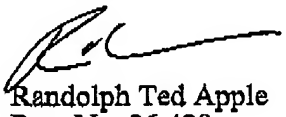
No prima facie case of obvious having been made, the claims should be allowed; Clarification of Record.

A mere assertion that an invention would have been obvious, unsupported by any evidence or scientific reasoning does not establish any legally cognizable basis for a rejection. The Office acknowledges that Houben does not describe the claimed invention. The Applicants believe it is beyond dispute that the secondary references relied on by the Office do not remedy the deficiencies of the Houben reference. The rationale provided for the instant rejection is that, because it is known that insulin can be used to treat hyperglycemia and glucagon can be used to treat hypoglycemia, and both may be administered to the same patient (i.e., used "in combination"), one of skill "would have been motivated" to make the claimed invention. Applicants respectfully submit that such vague, unsupported, and factually incorrect assertions do not provide basis for a rejection. At minimum, the Office *must present a convincing line of reasoning supporting a rejection*. See MPEP 2144; *Ex parte Clapp*, 227 USPQ 972, Bd. Pat. App. & Inter. 1985. Moreover, the Office is respectfully reminded that, to establish *prima facie* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. See MPEP 2143.03; *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). It is requested that, should the rejections be maintained in response to this submission, the Office clarify the record for appeal by explaining where the prior art teaches or suggests each of the claims and claim limitations.

In view of the foregoing remarks, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an

early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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